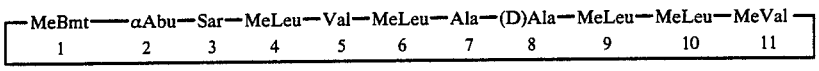
NOVEL CYCLOSPORINS

This is a continuation of application Ser. No. 932,760, filed Nov. 19, 1986, which in turn is a continuation of application Ser. No. 713,259, filed Mar. 19, 1985, both now abandoned.

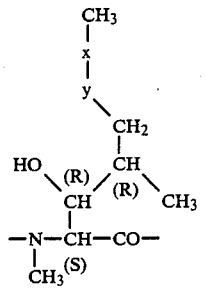
The present invention relates to novel cyclosporins, processes for their production, their use as pharmaceuticals and pharmaceutical compositions comprising them.

The cyclosporins comprise a class of structurally distinctive, cyclic, poly-N-methylated undecapeptides commonly possessing pharmacological, in particular immunosuppressive, anti-inflammatory and anti-parasitic activity. The first of the cyclosporins to be isolated and the "parent" compound of the class, was the naturally occurring fungal metabolite Cyclosporine, also known as cyclosporin A, of formula A



(A)

wherein —MeBmt— represents the N-methyl-(4R)-4-but-2E-en-1-yl-4-methyl-(L)threonyl residue of formula B



(B)

in which —x—y— is —CH=CH— (trans).

Since the original discovery of Cyclosporine a wide variety of naturally occurring cyclosporins have been isolated and identified and many further non-natural cyclosporins have been prepared by total- or semi-synthetic means or by the application of modified culture techniques. The class comprised by the cyclosporins is thus now substantial and includes for example the naturally occurring cyclosporins A through Z [c.f. Kobel et al. European Journal of applied Microbiology and Biotechnology 14, 237–240 (1982) and poster presented by Traber et al., 24th. Interscience Conference on Antimicrobial Agents and Chemotherpy, Washington, Oct. 8–10, (1984)]; as well as various non-natural or artificial cyclosporins, including dihydro-cyclosporins (in which the group —x—y— of the —MeBmt— residue—see formula B above—is saturated, e.g. as disclosed in U.S. Pat. Nos. 4,108,985; 4,210,581 and 4,220,641), cyclosporins in which the —MeBmt— residue is present in isomeric or N-desmethyl form [c.f. European Pat. No. 0 034 567 and "Cyclosporin A", Proc. Internat. Conference on Cyclosporin A, Cambridge (U.K.) September 1981, Ed. D. J. G. White, Elsevier Press (1982)—both describing the total-synthetic method for the production of cyclosporins developed by R. Wenger] and cyclosporins in which incorporation of variant amino acids at specific positions within the peptide sequence is effected (c.f. European Pat. No. 0 056 782). Examples of such cyclosporins as disclosed in the above art references include e.g. [Thr]^2—, [Val]^2—, [Nva]^2— and [Nva]^2—[Nva]^5—Cyclosporine (also known as cyclosporins C, D, G and M respectively), [Dihydro-MeBmt-]^1—[Val]^2—Cyclosporine (also known as dihydrocyclosporin D) and [(D)Ser]^8— and [Dihydro-MeBmt-]^1—[(D)-Ser]^8—Cyclosporine.

[In accordance with now conventional nomenclature for the cyclosporins, these are defined throughout the present specification and claims by reference to the structure of Cyclosporine (i.e. cyclosporin A). This is done by first indicating those residues in the molecule which differ from those present in Cyclosporine and then applying the term "Cyclosporine" to characterise the remaining residues which are identical to those present in Cyclosporine. At the same time the term —dihydro—MeBmt— is employed to designate the residue of formula B above in which —x—y— is —CH-$_2$—CH$_2$—. Thus [Dihydro—MeBmt]^1—[Val]^2—Cyclosporine is the cyclosporin having the sequence shown in formula A, but in which —MeBmt— [formula B, —x—y—=—CH=CH— (trans)] at the 1-position is replaced by —dihydro—MeBmt— [formula B, —x—y—=—CH$_2$—CH$_2$—] and —αAbu— at the 2-position is replaced by —Val—. Similarly [(D)Ser]^8—Cyclosporine is the cyclosporin having the sequence shown in formula A, but in which —(D)Ala— at the 8-position is replaced by —(D)Ser—.

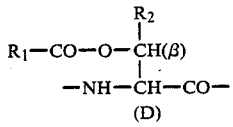
In addition, amino acid residues referred to by abbreviation, e.g. —Ala—, —MeVal— etc . . . are, in accordance with conventional practice, to be understood as having the (L)-configuration unless otherwise indicated. Residue abbreviations preceded by "Me", as in the case of —MeLeu— represent N-methylated residues. The individual residues of the cyclosporin molecule are numbered, as in the art, clockwise and starting with the residue —MeBmt— or —dihydro—MeBmt— in position 1. The same numerical sequence is employed throughout the present specification and claims.]

In accordance with the present invention it has now been found that novel cyclosporins may be obtained having pharmaceutical utility, in which the residue at the 8-position comprises an acyloxy α-amino acid residue having the (D)-configuration.

Accordingly, in its broadest aspect, the present invention provides: a cyclosporin wherein the amino acid residue at the 8-position is a (D)-acyloxy-α-amino acid residue, i.e. the residue of an α-amino acid of the (D)-series wherein the side chain attaching to the α-carbon atom is acyloxy-substituted.

Preferably the amino acid residue at the 8-position is a (D)-β-acyloxy-α-amino acid residue, i.e. the residue of an α-amino acid of the (D)-series having an acyloxy group attached at the β-carbon atom.

Preferred (D)-β-acyloxy-α-amino acid residues are those of formula II



(II)

(D)

wherein